

### **AMENDMENTS TO THE CLAIMS**

1. **(Original)** A method of modulating a biological response in a cell, the method comprising contacting the cell with at least one agent that modulates the expression or activity of  $\text{Err}\alpha$  or  $\text{Gabp}$ , wherein the biological response is
  - (a) expression of at least one OXPHOS gene;
  - (b) mitochondrial biogenesis;
  - (c) expression of Nuclear Respiratory Factor 1 (NRF-1);
  - (d)  $\beta$ -oxidation of fatty acids;
  - (e) total mitochondrial respiration;
  - (f) uncoupled respiration;
  - (g) mitochondrial DNA replication;
  - (h) expression of mitochondrial enzymes; or
  - (i) skeletal muscle fiber-type switching.
2. **(Original)** The method of claim 1, wherein the agent increases at least one of the biological responses.
3. **(Original)** The method of claim 1, wherein the agent modulates the formation of a complex between a PGC-1 polypeptide and (i) an  $\text{Err}\alpha$  polypeptide; or (ii) a  $\text{Gabp}$  polypeptide.
4. **(Currently Amended)** The method of ~~the preceding claim 3~~, wherein the agent increases the formation of the complex.
5. **(Currently Amended)** The method of claim 1, wherein the agent is an  $\text{Err}\alpha$  antagonist or an  $\text{Err}\alpha$  agonist.
6. **(Original)** The method of claim 1, wherein the agent modulates the expression level or the transcriptional activity of an  $\text{Err}\alpha$  polypeptide, a  $\text{Gabp}$  polypeptide, or of both.

7. **(Original)** The method of claim 1, comprising contacting the cell with two agents, wherein one agent modulates the expression or activity of *Errα* and the other agent modulates the expression or activity of *Gabp*.
- 8-10. **(Canceled)**
11. **(Original)** The method of claim 1, wherein the cell is in an organism.
12. **(Currently Amended)** The method of ~~the preceding~~ claim 11, wherein the organism is a mammal.
13. **(Currently Amended)** The method of ~~the preceding~~ claim 12, wherein the mammal is a human.
14. **(Currently Amended)** The method of ~~the preceding~~ claim 13, wherein the human is afflicted with a disorder characterized by reduced mitochondrial activity.
15. **(Currently Amended)** The method of ~~the preceding~~ claim 14, wherein the disorder is diabetes, obesity, cardiac myopathy, aging, coronary atherosclerotic heart disease, diabetes mellitus, Alzheimer's Disease, Parkinson's Disease, Huntington's disease, dystonia, Leber's hereditary optic neuropathy (LHON), schizophrenia, myodegenerative disorders such as "mitochondrial encephalopathy, lactic acidosis, and stroke" (MELAS). and "myoclonic epilepsy ragged red fiber syndrome" (MERRF), NARP (Neuropathy; Ataxia; Retinitis Pigmentosa), MNGIE (Myopathy and external ophthalmoplegia, neuropathy; gastro-intestinal encephalopathy, Kearns-Sayre disease, Pearson's Syndrome, PEO (Progressive External Ophthalmoplegia), congenital muscular dystrophy with mitochondrial structural abnormalities, Wolfram syndrome, Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy Deafness, Leigh's Syndrome, fatal infantile myopathy with severe mitochondrial DNA (mtDNA) depletion, benign "later-onset" myopathy with moderate reduction in mtDNA, dystonia, medium chain acyl-CoA dehydrogenase

deficiency, arthritis, ~~and~~ mitochondrial diabetes and deafness (MIDD), or mitochondrial DNA depletion syndrome.

16. **(Original)** The method of claim 1, wherein the cell is a skeletal muscle cell.
17. **(Original)** A method of determining if an agent is a potential agent for the treatment of a disorder that is characterized by glucose intolerance, insulin resistance or reduced mitochondrial function, the method comprising determining if the agent increases:
  - (i) the expression or activity of  $Err\alpha$  or  $Gabp$  in a cell; or
  - (ii) the formation of a complex between a PGC-1 polypeptide and (i) an  $Err\alpha$  polypeptide; or (ii) a  $Gabp$  polypeptide;wherein an agent that increases (i) or (ii) is a potential target for the treatment of the disorder.
18. **(Canceled)**
19. **(Currently Amended)** The method of claim ~~18~~ 17, wherein the agent increases the formation of the complex, and wherein the agent increases the biological response.
20. **(Original)** The method of claim 19, wherein the agent decreases the formation of the complex, and wherein the agent decreases the biological response.
21. **(Original)** The method of claim 18, wherein the contacting step is performed on a cell.
- 22-34. **(Canceled)**
35. **(Original)** A method of reducing the metabolic rate of a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of an agent which decreases the expression or activity of at least one of the following:
  - (i)  $Err\alpha$ ;
  - (ii)  $Gabpa$ ;

- (iii) a gene having an Err $\alpha$  binding site, a Gabpa binding site, or both; or
- (iv) a transcriptional activator which binds to an Err $\alpha$  binding site or to a Gabpa binding site;

thereby reducing the metabolic rate of the patient.

- 36. **(Original)** The method of claim 35, wherein the subject is afflicted with a viral infection or with cancer.
- 37. **(Currently Amended)** The method of ~~the preceding~~ claim 35, wherein the viral infection is a human immunodeficiency virus infection.
- 38. **(Original)** The method of claim 35, wherein the subject is afflicted with cancer cachexia, pulmonary cachexia, cardiac cachexia, Russell's Diencephalic Cachexia, or chronic renal insufficiency.
- 39-41. **(Canceled)**
- 42. **(Original)** A method of identifying a susceptibility locus for a disorder that is characterized by reduced mitochondrial function, glucose intolerance, or insulin intolerance in a subject, the method comprising
  - (i) identifying at least one polymorphisms in a gene, or linked to a gene, wherein the gene (a) has an Err $\alpha$  binding site, a Gabpa binding site, or both; or (b) is Err $\alpha$ , Gabpa, or Gabpb;
  - (ii) determining if at least one polymorphism is associated with the incidence of the disorder,wherein if a polymorphism is associated with the incidence of the disorder then the gene having the polymorphism, or the gene to which the polymorphism is linked, is a susceptibility locus.
- 43. **(Original)** The method of claim 42, wherein the gene is anyone of the gene listed on Tables 10-12.

44. **(Original)** The method of claim 42, wherein the disorder is a metabolic disorder.
45. **(Currently Amended)** The method of ~~the preceding claims~~ claim 44, wherein the disorder is diabetes or obesity.
46. **(Original)** The method of claim 44, wherein the metabolic disorder is a disorder associated with aberrant lipogenesis.
47. **(Currently Amended)** A method of determining if a subject is at risk of developing a disorder which is characterized by reduced mitochondrial function, the method comprising determining if a gene from the subject contains a mutation which reduces the function of the gene, wherein the gene has an  $\text{Error}$  binding site, a Gapba binding site, or both, wherein if a gene from the subject contains ~~[[a]]~~ the mutation then the subject is at risk of developing the disorder.
48. **(Currently Amended)** The method of ~~the preceding~~ claim 47, wherein the mutation reduces the function of the gene.
- 49-77. **(Canceled)**
78. **(Original)** A method of detecting statistically-significant differences in the expression level of at least one biomarker belonging to a biomarker set, between the members of a first and of a second experimental group, comprising:
- (a) obtaining a biomarker sample from members of the first and the second experimental groups;
  - (b) determining, for each biomarker sample, the expression levels of at least one biomarker belonging to the biomarker set and of at least one biomarker not belonging to the set;

- (c) generating a rank order of each biomarker according to a difference metric of its expression level in the first experimental group compared to the second experimental group;
- (d) calculating an experimental enrichment score for the biomarker set by applying a non parametric statistic; and
- (e) comparing the experimental enrichment score with a distribution of randomized enrichment scores to calculate the fraction of randomized enrichment scores greater than the experimental enrichment score, wherein a low fraction indicates a statistically-significant difference in the expression level of the biomarker set between the members of the first and of the second experimental group.

79-92. (Canceled)

93. **(Original)** A method of identifying an agent that regulates expression of OXPHOS-CR genes, the method comprising
- (a) contacting (i) an agent to be assessed for its ability to regulate expression of OXPHOS-CR genes with (ii) a test cell; and
  - (b) determining whether the expression of at least two OXPHOS-CR gene products show a coordinate change in the test cell compared to an appropriate control, wherein a coordinate change in the expression of the OXPHOS-CR gene products indicates that the agent regulates the expression of OXPHOS-CR genes.

94-105. (Canceled)

#### **REMARKS**

Claims 1-105 were pending in the subject application. Claims 8-10, 18, 22-34, 39-41, 49-77, 79-92 and 94-105 have been to reduce the excess-claims fees. Claims 5, 12-15, 19, 37, 45, 47 and 48 have been amended to clarify the claim dependencies. This amendment does not introduce new matter. Applicant respectfully requests entry of the subject amendment such that claims 1-7, 11-17, 19-21, 35-38, 42-48, 78 and 93 will be pending.